

REMARKS

Reconsideration is requested.

Claims 24-54 are pending. Claims 29, 31-33, 38, 41, 46, 48 and 49 have been allowed. The applicants acknowledge, with appreciation, the Examiner's indication that Claims 28, 30, 44, 45, 47 and 51-54 contain allowable subject matter (i.e., claims having been objected to as being dependent on a rejected base claim).

The specification has been amended again to include an updated reference to the parent applications. The undersigned notes that the request to amend the specification in this regard on the undersigned's cover sheet of July 6, 2001 was incomplete in not referring to two of the priority U.S. applications. The Examiner has acknowledged receipt of the foreign priority documents in the parent application Serial No. 08/256,568 (see, page 1 of the Office Action dated August 4, 2003) such that the undersigned presumes the Examiner has reviewed this parent application and the file history of the same. The Examiner is requested to advise the undersigned in the event anything further is required in this regard. A separate Request for a Corrected Filing Receipt is attached to specifically request that the Patent Office records are updated with regard to the parent applications.

The Examiner is requested to acknowledge the applicants claim for domestic priority in the Examiner's next Communication.

The specification and figures have been amended above to include a third sheet of Figure 2 (included herewith as new Figure 2B) which was included with the originally-filed PCT application (PCT/EP93/03325), from which the present application claims

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benefit. See, the attached copy of 17 sheets of drawings from the published PCT application (WO 94/12670).

The present application claims benefit of intermediate applications Serial Nos. 09/378,900 and 09/044,665, which issued as U.S. Patent Nos. 6,495,670 and 6,051,696, respectively. Each of these applications fails to include the additional sheet of Figure 2 (i.e., Figure 2B in the attached revised figures).

The parent PCT application (i.e., PCT/EP93/03325) was filed with a complete set of drawings.

The U.S. national phase of the PCT application (i.e., Serial No. 08/256,568) was also filed with a complete set of drawings. See, the attached excerpt from the Patent Office copy of the file history of Serial No. 08/256,568, as well as the file jacket from the same indicating that 17 sheets of drawings were filed.

A review of the file history of the parent application Serial No. 08/256,568, suggest however that once formal drawings were filed prior to issuance of the parent U.S. Patent No. 5,846,704, the second of three sheets of Figure 2 was omitted. U.S. Patent No. 5,846,704, therefore also does not include, as issued, a complete set of figures.

The application which issued as parent U.S. Patent No. 6,495,670 and 6,051,696, were apparently filed with the set of drawings used for formal purposes or based on the figures used for formal purposes in the parent application which issued as U.S. Patent No. 5,846,704. This apparent inadvertent error has only recently been appreciated and the applicants are moving to request correction of the parent patents separately.

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Inclusion of the missing sheet of Figure 2 is not believed to add new matter. The Examiner is requested to consider the following in this regard.

Figure 2, as originally-filed in the PCT application, and attached, includes an alignment of the 5' UR nucleotide sequences of isolates from four types of HCV. See, page 29, lines 13-15 of the specification.

The specification teaches that Figure 2 includes nucleotides in the region from -291 through -55 such that the sequences shown in the attached sheet Figure 2B would be expected to be included. See, page 38, lines 28-29 of the specification.

The third sheet of Figure 2, which was filed as FIG. 2B with the Amendment of December 12, 2001 and the originally-filed application (attached hereto as redesignated Figure 2C), describes all of the isolates included in the attached additional sheet Figure 2B. Moreover, the sequences shown in the additional sheet Figure 2B attached are direct continuations of the 5' UR region of the sequences (i.e., continuing from positions -147 through -219).

The sequences in the regions described in the additional sheet Figure 2B are moreover referred to in the specification and/or were publicly available at the time the present application was filed.

Specifically, the applicants note that the isolates HCV1, HCVJ, HCVJ6, HCVJ8 and BR56 were deposited and are available through Accession Nos. M62321, D10749, D00944, D01221 and D13348, respectively, as described, for example, on page 30, lines 1-16 and page 35, lines 4-5 of the specification. The sequences of isolates BU74 and BU79 are available through Accession Nos. D13449 and D13450, respectively, as disclosed at page 35, lines 5-6 of the specification. The sequence of isolate E-b8 is

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available through Accession No. D10116 and is identifiable through a search of Genbank. The sequence of isolate Z6 is described, for example, in Bukh et al. (1992 PNAS 89:4942-4946). See, page 38, lines 18-19 of the specification. Finally, the sequences of GB80 and GB81 are available through deposit Accession Nos. D13451 and D13452, respectively, as disclosed on page 35, lines 6-8 of the specification. Many of these sequences are further described and available in Chan et al. (Journal of General Virology (1992), 73, 1131-1141), of record.

Further support for the additional sheet of drawings may be found, for example, on page 9, lines 3-4 of the specification wherein a region extending from nucleotide position -170 to nucleotide position -155 is indicated as being contained in Figure 2. Moreover, the specification describes that Figure 2 contains a conserved region between -220 and -180. See, page 30, lines 14-15 of the specification. This conserved region is shown in the additional sheet of Figure 2 attached as Figure 2B.

The boxed regions in the attached Figure 2B extending from position -170 to position -155 and the corresponding SEQ ID NOs:5, 13 and 17 are described, for example, on pages 9-11 and specifically page 11, lines 15-32 of the specification. The boxed region and SEQ ID NO:27 in the attached sheet Figure 2B is also described on page 10 of the originally-filed application.

No new matter has been added. Entry of the attached three sheets of Figure 2 in place of the previously filed two sheets of Figure 2 is requested along with the further formal drawings attached.

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The additional formal drawings have been added for completeness and to include sequence identifiers corresponding to the attached Sequence Listing. Acceptance of the attached formal drawings in the Examiner's next Action is requested.

The specification has been amended to include the attached Sequence listing.

The attached paper and computer readable copies of the Sequence Listing are the same. No new matter has been added. A separate Statement to this effect is attached.

The specification has been amended to include the attached Sequence Listing, as required by the Examiner on ¶2 of the Office Action dated August 4, 2003 (Paper No. "072303" - as indicated on page 1 of the Office Action). The Examiner is requested to advise the undersigned in the event anything further is required to comply with the Sequence Listing requirements.

The Section 102 and alternative Section 103 rejections of claims 26 and 27, 36-37 and 40 over Sommer (Nucleic Acid Research, 17(16):6749 (1989)), are traversed. Reconsideration and withdrawal of the rejections are requested in view of the following distinguishing comments.

The presently claimed invention provides, in claim 26, for example, an isolated polynucleic acid consisting of 10 to 50 nucleotides which specifically hybridizes with the sequence of SEQ ID NO:20. The presently claimed invention provides, in claim 27, for example, an isolated polynucleic acid consisting of 27 to 50 nucleotides which specifically hybridizes with the sequence of SEQ ID NO:27, or the complement thereof. The presently claimed invention provides, in claim 37, for example, an isolated polynucleic acid consisting of 15 to 50 nucleotides which specifically hybridizes with at least one of SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3. The presently claimed

invention provides, in claim 40, for example, an isolated polynucleic acid consisting of 21 to 50 nucleotides which specifically hybridizes with the sequence of SEQ ID NO:20, or the complement thereof.

The Examiner asserts that Sommer teaches that "all that is required for specific priming (i.e., hybridization) is a sequence of 5'-GCC-3 somewhere in the target oligo. Note that each of SEQ ID NO:20 comprises the sequence 5'-GCC-3 at nucleotide positions 9-11." See, page 4 of Paper No. 072303. The Examiner concludes that "it can be said that Sommer et al. teach an isolated polynucleic acid which will specifically hybridize with SEQ ID NO:20." Id. Similar arguments are provided by the Examiner with regard to alleged anticipation and/or obviousness of sequences which will hybridize to SEQ ID NOs: 27, 1, 2 and 3. Id.

While "it can be said" that Sommer teaches as much as the Examiner believes, the same would not be the interpretation of one of ordinary skill in the art. Specifically, while Sommer may teach that "primers with a length between 17-20 nt need at least three homologous nucleotides at their 3' end for successful priming", and "primers to be employed in claiming homologous genes [should have the following criteria] the length should be preferably between 20-24 nt and the 3' nucleotides should match completely" Sommer does not teach that this is all that is required, as apparently interpreted by the Examiner. In fact, as explained below, the applicants believe the specific priming described by Sommer, which the Examiner equates to hybridization, is determined by a combination of overall percent identity of the primer with the target sequence and perhaps the number of 3' nucleotides of the primer which exactly match the target sequence.

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Specifically, the following Table summarizes the information from Table 1 of Sommer and details, for each primer the length of the primer, the number of 3' nucleotides of the primer which exactly match the target sequence, the overall percent identity of the primer with the target sequence and the "amplification efficiency" as indicated by Sommer.

Primer	Length (nts)	No of 3' nts of primer exactly matching target sequence	Overall % identity of primer with target sequence	Amplification efficiency
a	17	0	82	-
b	17	0	82	-
c	17	3	47	+
d	17	4	47	+
e	17	1	76	-
f	17	2	76	++
g	17	3	71	++
h	17	9	65	+
i	17	6	59	+
k	17	3	53	+
l	17	8	88	++
m	20	2	70	-
n	36	2	61	+

The following will be appreciated from the above.

Primer "n" has only 2 nts at its 3' end that are exactly matching the target sequence and yet the amplification efficiency of primer n is rated "+". Primer "n" is more than the 17-20 nt long primer which is specifically mentioned by Sommer. Moreover, primer "n" is 61% identical with the target sequence of 36 nucleotides. Accordingly, Sommer's conclusions, if valid for primers of 17-20 nt, which the applicants do not believe to be true, are not applicable to primers of greater (or lesser) length.

Primers c, g, and k (all 17 nts in length) all have 3 nts at their 3' end that are exactly matching the target sequence. Yet, there is a marked difference between amplification efficiency with primer g (rated "++") and primers c and k (both rated "+"). There must thus be additional elements or factors (other than three 3' exactly matching nts) contributing to the hybridization efficiency of a probe/primer to its target sequence.

One such element is likely the overall percent identity of a probe/primer with its target sequence: for primer g this is 71%, while for primers c and k these are 47% and 53%, respectively. Thus, the higher the overall percent identity for the otherwise "identical" probes/primers (identical for length and for having 3 exactly matching 3'nts), the greater the specificity of hybridization of said probe/primer with its target sequence. More is therefore required than merely a 3 nt 3' match for even primers of 17-20 nts.

Following the overly broad interpretation of the Examiner of Sommer et al. 1989, i.e., that only 3 exactly matching 3'nts are sufficient for specific hybridization of a probe/primer with its target sequence, the Examiner would presumably expect that greater hybridization specificity would be obtained if more 3'nts exactly match with the target sequence were included in the primer. The following two examples are, however, in contradiction with this expectation:

- Primers d and i (having 4 and 6 exactly matching 3'nts, respectively) perform less well than primer g (having 3 exactly matching 3'nts). Note that the overall percent identity of primers d and i to their target sequence (47% and 59%, respectively) is lower than the percent identity of primer g to its target sequence (71%), see also comments above with regard to primers c, g and k.
- Primers h and l apparently are the only primers of Sommer et al. performing as well as primer g but these primers have 9 and 8 exactly matching 3'nts, respectively. This is thus by far exceeding the minimum requirement of 3 exactly matching 3'nts of primer g.

It thus appears that primer g is an exception rather than the rule and the Examiner's interpretation (i.e., that only three 3' nts are required) of Sommer's conclusions (i.e., that at least three 3' nts are required) is in error.

Further, following the broad interpretation of the Examiner of Sommer et al. 1989, i.e., that only 3 exactly matching 3'nts in a probe/primer are sufficient for specific hybridization of that probe/primer to its target sequenced, one would expect, incorrectly, that the overall percent identity of any probe/primer to its target sequence would have to be only between 8% (3/36 for active primer n of Sommer et al.; note that this should in fact be 6%, i.e., 2/36, see comments above with regard to primer "n") and 18% (3/17). None of the primers of Sommer et al., however, fulfill this requirement as the minimum percent identity of an active primer of Sommer with at least 3 exactly matching 3'nts is 47% (see primer c).

The Examiner's interpretation of Sommer and application of the same to reject claims 26-27, 36-37 and 40 as being unpatentable is, with due respect, unfounded. The rejections of claims 26-27, 36-37 and 40 over Sommer should be withdrawn.

Withdrawal of the Section 102 and Section 103 rejections of claims 26-27, 36-37 and 40 over Sommer is requested.

The Section 103 rejection of claim 34 as allegedly being obvious over Sommer in view of the Stratagene Catalog (1988), is traversed. Reconsideration and withdrawal of the rejection are requested for the reasons noted above. Specifically, the Stratagene reference fails to cure the deficiencies of Sommer noted above. Withdrawal of the Section 103 rejection of claim 34 is requested.

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The Examiner is requested to hold in abeyance the obviousness-type double patenting rejections until such time as the claims are otherwise indicated as being allowable. The applicants will then consider filing a Terminal Disclaimer to obviate the rejections and the Examiner is requested to contact the undersigned, preferably by telephone, to facilitate the consideration of the same in the event the present Amendment otherwise places the application in condition for allowance.

For completeness however, the applicants respectfully request reconsideration and withdrawal of the obviousness-type double patenting rejections stated in ¶¶11 and 14 of Paper No. 072303 as the Examiner's reliance on a secondary reference (i.e., Stratagene (1988)) as a basis for the rejection is believed to be inappropriate. Obviousness-type double patenting rejections are based on the assertion that the claims of the prior patent would have made the pending claims obvious. Just as an Examiner is not permitted to rely on the specification of a prior patent in rejecting subsequent claims under the judicially-created doctrine of obviousness-type double patenting, an Examiner should not be permitted to rely on a secondary reference as a basis for an obviousness-type double patenting rejection. At a minimum, reconsideration and withdrawal of the rejections stated in ¶¶11 and 14 of Paper No. 072303 is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is requested to contact the undersigned if anything further is required in this regard.

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Respectfully submitted,

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